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Medicines Evidence Commentary

commentary on important new evidence from Medicines Awareness Weekly

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Coronary stenting: duration of dual antiplatelet therapy

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The PRODIGY trial found that dual antiplatelet therapy with clopidogrel and aspirin for 24 months after coronary stenting was not significantly more effective in reducing a composite of death, myocardial infarction or cerebrovascular accident than 6 months of dual therapy. There was an increased risk of bleeding requiring medical or surgical intervention with 24 months, compared with 6 months of dual therapy. It is therefore important that patients are reviewed and do not continue to take dual antiplatelet therapy for longer than is considered beneficial.

Overview and current advice

Dual antiplatelet therapy (usually a combination of clopidogrel and aspirin) is recommended following implantation of coronary stents to reduce the risk of stent thrombosis. After a period of time the clopidogrel should be discontinued and treatment continued with aspirin alone. However, the optimal duration of dual therapy has not been clearly identified in clinical trials.

NICE guidance on drug-eluting stents for the treatment of coronary artery disease[1] does not recommend any specific duration of dual antiplatelet therapy with clopidogrel and aspirin after implantation of a drug-eluting stent. NICE refers to US recommendations[2] which advise a duration of at least 12 months, after which time the need for clopidogrel should be reviewed, taking into account the risk for further events on an individual patient basis.

For people undergoing bare-metal stenting, US guidelines recommend dual antiplatelet therapy for 12 months in acute coronary syndrome, and for a minimum of one month and ideally up to 12 months in patients with stable coronary artery disease[2]. The evidence review group that developed NICE guidance on ticagrelor for the treatment of acute coronary syndromes concluded that standard practice for STEMI should include dual antiplatelet therapy for 3 months for patients undergoing revascularisation with bare-metal stents[3].

New evidence

This new study[4] assessed the effect of dual antiplatelet therapy with clopidogrel and aspirin for 6 versus 24 months in people receiving bare-metal or drug eluting (everolimus, paclitaxel, or zotarolimus) stenting. This randomised controlled trial (n=2013) included individuals with chronic stable coronary artery disease and acute coronary syndrome. It found no significant efficacy benefit with use of dual antiplatelet therapy with clopidogrel and aspirin for 24 months, compared with 6 months, in reducing the primary composite outcome of death from any cause, myocardial infarction or cerebrovascular accident at 2 years. The event rate for the primary outcome was 10.0% in the 6-month clopidogrel group and 10.1% in the 24-month clopidogrel group (hazard ratio [HR] 0.98, 95% confidence interval [CI] 0.74 to 1.29, p=0.91). There was also no significant difference between the groups in any of the secondary efficacy outcomes, which included the individual components of the primary outcome[4].

Regarding bleeding, dual antiplatelet therapy for 24 months approximately doubled the number of bleeding events requiring intervention, which included events that required medical or surgical treatment, transfusion and life-threatening events, compared with 6 months of dual therapy (bleeding event rate 7.4% in 24 month treatment group, 3.5% in 6 month treatment group; HR 2.17, 95% CI 1.44 to 3.22, p=0.00018)[4].

A problem with all clinical trials is the balance between the reliability of the results and the extent to which they can be applied to normal clinical practice[5]. A strength of this study is its pragmatic design. It recruited 'all-comers' with broad selection criteria to reflect routine clinical practice where people demonstrate variable adherence to drug regimens, have a number of co-morbid conditions, and use a number of other medications[5]. However, this also led to some important limitations. The study had an open-label design and treatment allocation was not concealed. Both of these could have introduced selection and evaluation bias. However, all ischaemic and bleeding events were adjudicated centrally by an independent committee who were unaware of the treatment-group assignments. Finally, interpretation and application of the results to current practice is confounded by the inclusion of both newer and older generation drug-eluting stents and bare metal stents.

Commentary

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The optimal duration of dual antiplatelet therapy and the risk-benefit ratio of long-term dual antiplatelet therapy after coronary stenting have not been clearly identified in clinical trials. This 2 year study of approximately 2000 people aimed to address these important issues. It found that continuing clopidogrel for 24 months after coronary stenting did not improve patient outcomes compared with 6 months dual therapy, but approximately doubled the risk of bleeding requiring medical or surgical intervention. Although more patients in the 6-month clopidogrel group discontinued clopidogrel treatment after the first month, compared with the 24-month group (12% vs. 0.2%), which might be expected to affect the bleeding rate, other studies such as CURE[6] have also shown that combined use of aspirin and clopidogrel is associated with a greater bleeding risk than aspirin alone. It is therefore important that patients are reviewed and do not continue to take dual antiplatelet therapy for longer than is considered beneficial.

Previous studies have shown a benefit for up to 12 months of dual therapy[7,8], but evidence supporting its use beyond 12 months is limited[9]. This study compared continuing clopidogrel with aspirin for 24 months after coronary stenting with 6 months dual therapy, rather than for the 12 months that is more usual in clinical practice. Although the longer duration of treatment did not improve patient outcomes in this study, further evidence is needed before less than 12 months of dual therapy after coronary stenting can be recommended routinely. Shorter durations may be appropriate for some people on an individual patient basis, particularly those with stable coronary artery disease receiving a bare-metal stent or those with significant risk factors for bleeding.

Other antiplatelets, ticagrelor and prasugrel, are now being used to treat acute coronary syndromes in conjunction with aspirin for 12 months and it is not known whether treatment with these agents for more than 12 months would be beneficial for patients who have stents inserted.

The limitations of the PRODIGY study mean that, while it provides support to the argument that dual antiplatelet therapy can be less than 12 months duration with the latest generation drug-eluting stents, it is by no means robustly conclusive. There are a number of on-going studies looking at both prolonged and shortened periods of dual antiplatelet therapy (e.g. DAPT, n>20,000, 12 months vs 30 months; OPTIMIZE, n~3120, 3 months vs 12 months; ISAR–SAFE, n~6000, 6 months vs 12 months). These trials aim to determine the balance between efficacy in preventing stent thrombosis and the risk of bleeding associated with prolonged dual anti-platelet therapy. Their results may help to further inform practice.

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